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PCT/GB00/03851

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

GILL JENNINGS & EVERY
 Broadgate House
 7 Eldon Street
 London EC2M 7LH
 ROYAUME-UNI

Date of mailing (day/month/year) 26 March 2002 (26.03.02)	
Applicant's or agent's file reference REP06248WO	IMPORTANT NOTIFICATION
International application No. PCT/GB00/03851	International filing date (day/month/year) 06 October 2000 (06.10.00)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address BURK, Mark, Joseph Apartment 115 1610 Nantucket Circle Santa Clara, CA 95054 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address BURK, Mark, Joseph 12634 Intermezzo Way San Diego, CA 92130 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

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3. Further observations, if necessary:

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Anne BEUCHAT Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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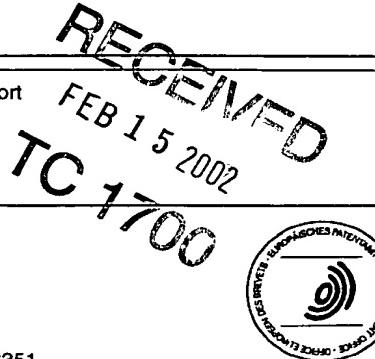
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REP06248WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/03851	International filing date (day/month/year) 06/10/2000	Priority date (day/month/year) 08/10/1999
International Patent Classification (IPC) or national classification and IPC B01J31/22		
<p>Applicant CHIROTECH TECHNOLOGY LIMITED et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 23/03/2001	Date of completion of this report 08.01.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schwaller, J-M Telephone No. +49 89 2399 8351



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03851

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-10 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/03851

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-14
	No:	Claims
Inventive step (IS)	Yes:	Claims 12 + 1 + 2 + 14
	No:	Claims 1-14
Industrial applicability (IA)	Yes:	Claims 1-14
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03851

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: Burk M.J. et al., *Tetrahedron Letters*, 35, (1994), pages 4963-4966

D2: WO-A-9828074

2. The **(too broad)** subject-matter claimed does not meet the requirements of Article 33 PCT for the following reasons:

- 2.1 Document D1, which is considered to represent the most relevant state of the art, discloses a dialkylphosphinoferrocene bearing a cationic rhodium (I) complex suitable for hydrogenating aldehydes and ketones.
- 2.2 The subject-matter of present claim 1 **differs therefrom** in that the catalyst is supported on a heterogeneous supporting medium that provides anionic binding sites.
- 2.3 The **problem to be solved** by the present invention may therefore be regarded as providing a higher hydrogenation activity and selectivity.
- 2.4 The **solution proposed** in claim 1 of the present application, namely supporting the catalyst on a heterogeneous supporting material having anionic binding sites, **cannot be considered as involving an inventive step (Article 33(3) PCT)** because this feature is described in document D2 (see the passages cited in the search report) as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal design option to include this feature in the catalyst and process described in document D1 in order to solve the problem posed.

It is furthermore noted that there is **no comparison** in the present specification with the same catalyst without supporting material, so that the alleged effect is totally speculative and in no way supported by any evidence.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/03851

3. In view of the argumentation provided by the Applicant during the international preliminary examination procedure, a **process** claim including all the features of present claims 12, 1, 2 and 14 would nevertheless appear to meet the requirements of Article 33 PCT because the use of the thus claimed specific type of catalyst in the presence of water as a co-solvent improves the chemoselectivity in the hydrogenation of functionalised aldehydes.

Re Item VIII

Certain observations on the international application

It is clear from the argumentation provided by the Applicant and the Examples that the presence of water as a co-solvent is **essential** to solve the problem addressed in the application.

Since the independent claim 12 does not contain this feature the application does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3 (b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



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19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
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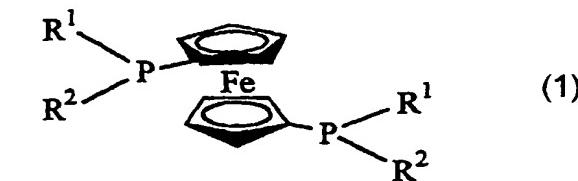
- (51) International Patent Classification⁷: **B01J 31/22, 31/28, C07C 45/62**
- (21) International Application Number: **PCT/GB00/03851**
- (22) International Filing Date: **6 October 2000 (06.10.2000)**
- (25) Filing Language: **English**
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- (30) Priority Data:
9923952.7 8 October 1999 (08.10.1999) GB
- (71) Applicant (for all designated States except US): **CHIROTECH TECHNOLOGY LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 0WG (GB).**
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **BURK, Mark, Joseph [US/US]; Apartment 115, 1610 Nantucket Circle, Santa Clara, CA 95054 (US). GERLACH, Arne [DE/GB]; Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0WG (GB).**
- (74) Agent: **GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).**
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**

Published:

— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/26807 A1



(54) Title: SUPPORTED FERROCENE-BASED CATALYSTS FOR SELECTIVE ALDEHYDE HYDROGENATION

(57) Abstract: A supported catalyst comprises a cationic rhodium (I) complex of formula (1) wherein R¹ and R² are the same or different hydrocarbon groups of up to 30 C atoms, or R¹ and R² are linked to form a ring, and a heterogeneous support medium that provides anionic binding sites. Such a complex is particularly useful as a catalyst in a process of hydrogenating an aldehyde to produce the corresponding primary alcohol.

SUPPORTED FERROCENE-BASED CATALYSTS FOR SELECTIVE ALDEHYDE HYDROGENATION

Field of the Invention

5 This invention relates to a supported catalyst and to its use, e.g. in the efficient and selective hydrogenation of aldehydes to alcohols.

Background of the Invention

Both homogeneous and heterogeneous catalysts are known, as are their respective advantages and disadvantages. One way of combining the features of both is to immobilise or tether a homogeneous catalyst to a polymeric or inorganic solid support. An undesirable aspect of this strategy is that the heterogenised ligand systems often are very tedious and/or expensive to prepare. Another problem is that polymer-supported homogeneous catalysts frequently have reduced catalytic activities and selectivities relative to the unsupported homogeneous analogues. Upon attempted reuse, the activities and 10 selectivities of these catalysts are often reduced further. Finally, many immobilised homogeneous catalysts suffer from a high degree of metal loss from the support (leaching) during use; see, for example, Lindner, *et al, Angew. Chemie Int. Ed.* 1999, 38, 2155.

20 Aldehyde reduction often is a desirable step in obtaining valuable alcohol products from inexpensive starting materials (e.g., alkenes, hydrogen and carbon monoxide in the case of hydroformylation). Despite the importance of aldehyde reduction in organic chemistry, surprisingly few generally applicable manufacturing methods are available for this transformation. Hydride reducing agents (e.g. LiAlH₄ or NaBH₄) are widely used, but are moisture-sensitive reagents that are not economically attractive for commercial procedures since they are employed in stoichiometric quantities. Moreover, their use 25 requires tedious work-up procedures and generates substantial quantities of waste (boron or aluminium salts).

Numerous heterogeneous catalysts, such as PtO₂, Raney Ni, and Pd/C, can catalyse the reduction of specific aldehydes. However, heterogeneous catalysts are often intolerant of various organic groups such as divalent sulfides. Moreover, other sensitive groups such 30 as nitro, oxime, ketone, aryl halide or benzyloxy, also are reduced. Another problem encountered when reducing aromatic aldehydes using heterogeneous catalysts is that the

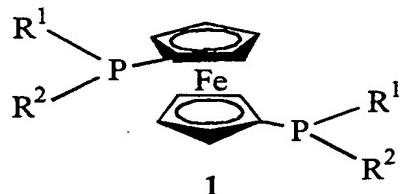
product may be further reduced to a methyl substituent. For example, heterogeneous hydrogenation of benzaldehyde often affords toluene.

Very few practical homogeneous systems efficiently catalyse aldehyde hydrogenation. Problems often encountered include low reaction rates and/or catalyst deactivation due to aldehyde decarbonylation processes.

The use of cationic rhodium catalysts for aldehyde hydrogenation has been reported by Tani *et al*, *Chem. Lett.* 1982, 261, and by Burk *et al*, *Tetrahedron Lett.* 1994, 35, 4963. Results suggest that the achievement of high efficiency in rhodium-catalysed aldehyde hydrogenation requires the use of electron-rich (dialkyl- or trialkyl-substituted) chelating phosphine ligands, but these tend to be very air-sensitive and are not suitable for industrial manufacture. Burk *et al.* describes an electron-rich, yet air-stable crystalline ligand, 1,1'-bis(diisopropylphosphino)ferrocene (DiPFc) 1 ($R^1 = R^2 = i\text{-Pr}$). The homogeneous rhodium catalyst (DiPFc-Rh) also is stable to oxygen and has been shown to hydrogenate a limited set of aldehydes with high reaction rates.

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A new method of anchoring certain rhodium catalysts to solid supports has recently been described by Augustine *et al*, *Chem. Comm.* 1999, 1257. This simple procedure involves treating a readily available solid material (silica, alumina, carbon, etc.) with a heteropolyacid such a phosphotungstic acid, followed by addition of an appropriate catalyst precursor complex. Immobilised catalysts formed in this fashion were reported to serve as active and reusable catalysts for alkene hydrogenation.

Summary of the Invention

According to the present invention, an immobilised homogeneous catalyst is useful, *inter alia*, for the efficient and chemoselective hydrogenation of aldehydes. The catalyst system is based upon homogeneous rhodium complexes bearing phosphines of formula 1, wherein R^1 and R^2 are independently the same or different hydrocarbon substituents, e.g.

alkyl, substituted alkyl, arylalkyl or aryl, of up to 30 C atoms, or R¹ and R² are linked to form a ring. Preferably, R¹ and R² are alkyl groups and more preferably identical alkyl groups. The solid support provides anionic binding sites.

The utility of the novel catalyst is surprising, for various reasons. Firstly, it was 5 not evident that the complex could be supported. Secondly, its activity for aldehyde hydrogenation is good especially given the acidic nature of the support. Further, the immobilised hydrogenation catalyst can be effectively recovered and re-used.

Description of the Invention

Solid supports that are effective for use in the invention are those providing anionic 10 binding sites. The support may or may not be modified with a heteropolyacid anchoring agent. The support medium is preferably an oxide such as alumina, silica, carbon, montmorillonite, etc., and is preferably modified with a heteropolyacid. The heteropolyacid is preferably of the Keggin type, e.g. phosphotungstic acid, phosphomolybdic acid or silicotungstic acid. Alternatively, an anionic exchange resin such 15 as poly *para*-toluenesulfonic acid or Nafion in its acidic or anionic form may be used. For example, the support medium is a cation exchange resin containing sulphonate acid groups $-\text{SO}_3^- \text{X}^+$, wherein X⁺ is a proton or any other exchangeable cation. A preferred cation exchange resin is a tetrafluoroethylene-perfluoro(vinyl ether sulfonate) copolymer.

Many different types of aldehydes, e.g. of formula RCHO, wherein R is an organic 20 group up to 30 C atoms, may be hydrogenated to give RCH₂OH, using the novel catalyst. The aldehyde substrate may possess a range of different functional groups that either inhibit or react with commonly employed heterogeneous catalysts. Due to the acidic nature of the supports used in the immobilisation of the homogeneous catalyst, a non-standard solvent mixture may be required. The use of an alcohol/water mixture, and 25 particularly an isopropanol/water mixture, is preferred, so that the hydrogenation reaction proceeds to completion. In particular, acetal formation can be minimised or avoided. The immobilised catalyst system may be recovered by simple filtration and re-used in subsequent reactions.

In addition to the hydrogenation of aldehydes, a catalyst of the invention may also 30 be used for hydrogenation of other unsaturated groups. For example, unsaturated functionality such as the carbon-carbon double bond of alkenes, the carbon-carbon triple bond of alkynes, the carbon-oxygen double bond of ketones and the carbon-nitrogen

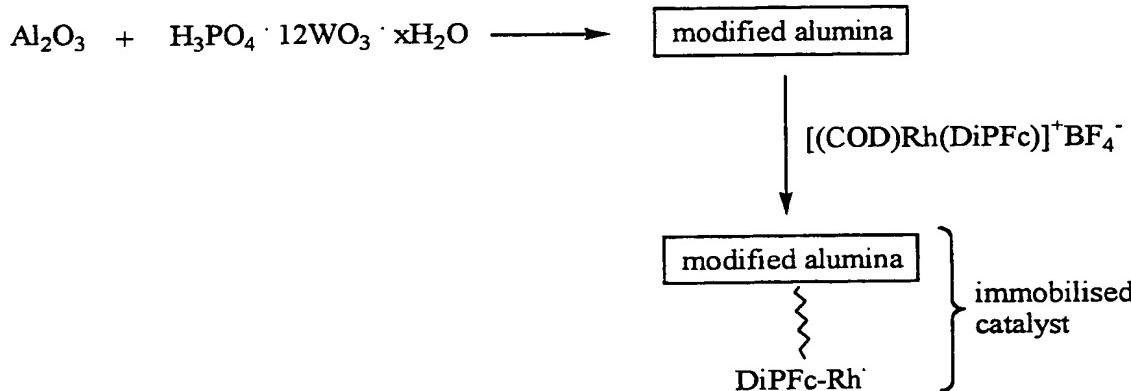
double bond of substrates such as N-acylhydrazones may be hydrogenated using these catalyst systems.

Some aldehydes are quite temperature-sensitive and decompose as the temperature is increased much above room temperature. In such cases, the ability to perform the 5 hydrogenation at mild temperatures is vital. Increasing the temperature may increase the reaction rate, but the novel catalyst may be performed over a broad temperature range of -30°C to +150°C. The preferred temperature is in the range 0°C to 60°C.

Performing reactions under low pressure is often preferred for manufacturing due to the fact that high-pressure equipment is more costly to purchase and operate. An 10 important advantage of this invention is that the catalyst can perform effectively under both high and low hydrogen pressures, e.g. over the range of 1 to 100 atmospheres (100 - 10000 kPa). Increasing the pressure may increase the reaction rates. The preferred pressure range will depend on the process being operated and the desired reaction rates.

Heterogenised rhodium catalyst systems bearing 1,1'-bis(dialkylphosphino)ferrocene ligands 1 may be prepared via various procedures. By way 15 of representative example, an immobilised catalyst may be formed by mixing neutral alumina with phosphotungstic acid in methanol, followed by the addition of the catalyst precursor $[(\text{COD})\text{Rh}(\text{DiPFc})]^+\text{BF}_4^-$ (see Scheme 1). After allowing the mixture to stir for a specified period, the rhodium complex is completely absorbed onto the solid support. 20 The tethered catalyst is then filtered, washed with methanol, and employed directly in catalysis. The mechanism of absorption and the exact nature of the tethered complex are unclear.

Scheme 1.



The DiPFc-Rh catalyst prepared as in Scheme 1 has been tested for effectiveness in the hydrogenation of a range of different multifunctional aldehydes. These studies were aimed at demonstrating the combined properties of high catalytic efficiency under mild 5 conditions, selectivity in the reduction process, and tolerance of the catalyst to certain functionality. The robust nature of the catalyst system also was important. Moreover, comparisons have been made with commonly employed heterogeneous catalysts such as palladium on carbon, platinum oxide, and palladium on barium sulfate.

The following Examples illustrate the invention.

10 Example 1

Preparation of [(DiPFc)Rh(COD)]X on modified silica

A solution of phosphotungstic acid (PTA, 288 mg, 0.1 mmol, 1.0 eq.) in 25 ml degassed methanol was added dropwise to a vigorously stirred (overhead stirrer was used to minimise grinding) suspension of 4.00 g silica (Silica gel 60 for flash chromatography 15 (Fluka), particle size 0.035-0.070 mm (220-440 mesh ASTM, activity according to Brockmann and Schrodter: 2-3) in 30 ml of degassed methanol under nitrogen. The resulting mixture was stirred for 1 hour at room temperature. Subsequently, a solution of [(DiPFc)Rh(COD)]BF₄ (64 mg, 0.09 mmol, 0.9 eq.) in 10 ml degassed methanol was dripped to the vigorously stirred slurry of the activated silica. Stirring was continued for 20 4.5 hours at room temperature. After solvent evaporation the remaining solid was placed in a Soxhlet apparatus and continuously extracted with degassed methanol under nitrogen for 16 hours. The orange silica powder was isolated, dried and stored under nitrogen as a precaution. Yield: 3.64 g (86%).

The alumina supported DiPFc-Rh catalyst was prepared by an analogous protocol 25 to that outlined above.

Example 2

General Hydrogenation Procedure

All reactions were carried out in a 50 ml Parr micro-reactor modified with an injection septum and valve. The micro reactor was used in connection with a suitable glass 30 liner. The solvent (2-propanol/water mixture; 1:1 v/v) was deoxygenated by bubbling nitrogen through it for 3 hours while stirring. The hydrogenation substrate and the immobilised catalyst were added to a 50 ml glass liner, which was then immediately placed

in a 50 ml Parr pressure vessel. This was then sealed and purged with hydrogen (5 pressurisation (690 kPa)/release cycles). Degassed solvent (2-propanol/water; 1:1 v/v) was then added *via* cannula, the reactor purged again with hydrogen (5 pressurisation (690 kPa)/release cycles), charged to the initial hydrogen pressure (690 kPa) and vigorously stirred at a constant temperature (ambient temperature or heating bath). After an allocated period of time (hydrogen uptake was monitored) hydrogen pressure was released, and the reaction mixture was filtered (separation from the supported catalyst). The filtrate was then extracted several times with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and evaporated. The product distribution of the crude product mixture was determined by $^1\text{H-NMR}$ spectroscopy and was compared with authentic samples of all products. In cases where the formation of water-soluble or volatile products was likely, the hydrogenation mixture also was analysed *via* HPLC prior to extractive work-up.

Thus, experiments were performed under a standard set of mild reaction conditions: conversion to product = 100%, hydrogen pressure = 690 kPa, temperature = 20°C, reaction time = 16 h, mol aldehyde/mol Rh = 300-500 (based upon analysis of Rh content), concentration = 0.1 M, solvent: 2-propanol/water (1:1 v/v). Analytical procedures and results are given in Table 1.

The results show that the catalyst was robust and would operate effectively under very mild reaction conditions. This is demonstrated by the fact that all experiments listed in Table 1 were conducted using catalyst that was stored under an atmosphere of air for a period of ten months. This immobilised homogeneous catalyst allowed complete hydrogenation of each aldehyde listed to afford exclusively the desired alcohol product in high yield. The results further reveal that aldehydes bearing either alkyl substituents (R = alkyl) or aromatic substituents (R = aryl) may be reduced with equal facility. Functional groups that are reduced by most common heterogeneous catalysts, including aryl halide, nitro, and benzyloxy, were not reduced.

In contrast, common heterogeneous catalysts invariably yielded mixtures of products due to low chemoselectivity in reduction of the aldehyde carbonyl group (substrates 7-9, 13). In all cases using the heterogeneous catalysts, milder than normal reaction conditions were employed in an effort to achieve some level of selectivity in the reduction process. This strategy provided the best advantage to the heterogeneous

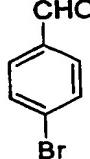
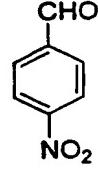
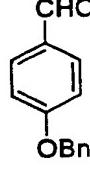
catalyst, but resulted in incomplete conversion of starting aldehyde in some cases. In all such cases, driving the reactions further to allow complete conversion of substrate led to lower selectivities.

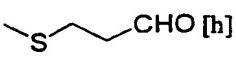
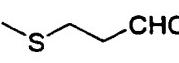
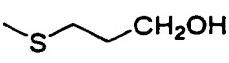
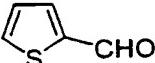
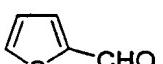
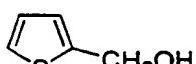
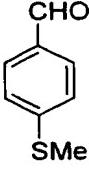
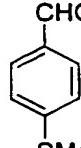
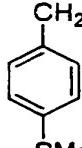
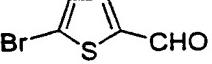
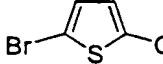
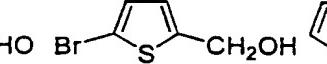
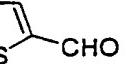
Importantly, the novel catalyst displayed broad tolerance to various organic 5 functionalities, including sulphur-containing groups, with no apparent diminution of catalytic rates. Sulphur functionality is notoriously detrimental to most heterogeneous catalysts, leading to serious levels of catalyst inhibition. This point was amply demonstrated in experiments 10-13. Of particular note is the successful hydrogenation of substrates 10 and 12, which contain non-aromatic sulfide groups.

10 In addition to a catalyst with an alumina solid support, identical results were achieved using a DiPFc-Rh catalyst anchored to silica in the fashion described above in Scheme 1 (see hydrogenation results involving substrate 12). The use of a silica support offers significant practical advantages since this immobilised catalyst system is more readily handled and removed from the reaction mixtures.

15 One advantage of an immobilised catalyst is the potential to remove it completely from the reaction mixture through filtration, and also to reuse the catalyst in subsequent processes. This is demonstrated by performing 4 successive hydrogenations involving 2-thiophene carboxaldehyde (substrate 11). This particular aldehyde bears sulfur functionality, which should test the robustness of the immobilised catalyst in the presence 20 of potential coordinating groups. In each case the hydrogenation was performed under conditions described in Table 1. After allowing the reaction to stir for 6 h (hydrogen uptake was monitored), a small sample was removed, and complete conversion to alcohol product was confirmed by ¹H NMR spectroscopy. The entire solution phase containing the product then was removed by syringe, the catalyst was washed twice with fresh 25 solvent, and a subsequent aliquot of hydrogenation substrate in 2-propanol/water was added. The immobilised catalyst was used successfully for four catalytic cycles, and complete conversion to the corresponding alcohol product was observed after each run. No reduction of catalytic activity was noted over the four cycles.

Table 1. Selective Aldehyde Hydrogenations

	Catalyst ^[a]	Product Distribution ^[b]	
			
6	DiPFc-Rh on alumina	n.d. ^[c]	100%
			
7	DiPFc-Rh on alumina	n.d.	100%
	dppb-Rh on silica	93%	7%
	Platinum oxide	1%	90%
	Pd on carbon	80%	n.d.
	Pd on carbon ^[d]	n.d.	n.d.
	Pd on barium sulfate ^[f]	85%	n.d.
			100% ^[e]
			15% n.d. ^[e]
			
8	DiPFc-Rh on alumina	n.d.	100%
	Pd on carbon	58%	0%
			42%
			
9	DiPFc-Rh on alumina	n.d.	100%
	Pd on carbon	n.d.	n.d.
			40% 60%

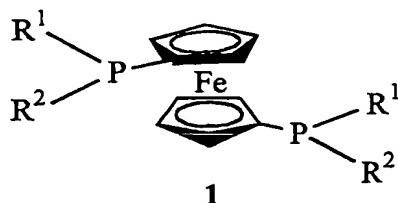
	Catalyst ^[a]	Product Distribution ^[b]		
				
10		n.d.	100%	
	DiPFc-Rh on alumina	n.d.	100%	
	Pd on carbon ^[i]	100%	n.d.	
	Platinum oxide ^[j]	>98%	<2%	
				
11		n.d.	100%	
	DiPFc-Rh on alumina	n.d.	100%	
	Pd on carbon ^[i]	92%	8%	
				
12		n.d.	100%	
	DiPFc-Rh on alumina	n.d.	100%	
	DiPFc-Rh on silica	n.d.	100%	
	DiPFc-Rh on silica ^[j]	n.d.	100%	
	DiPFc-Rh on silica ^[k]	69%	31%	
	dppb-Rh on silica	100%	0%	
	Platinum oxide ^[l]	3%	97%	
	Pd on carbon ^[i]	95%	5%	
				
13		40%	60%	n.d.
	DiPFc-Rh on alumina	40%	60%	n.d.
	Pd on carbon	17%	n.d.	83%

[a] Hydrogenation conditions for DiPFc-Rh on alumina or silica: 100 psi hydrogen, S/C > 300, 0.1 molar in 2-propanol - water (1:1), room temperature, overnight; conditions for dppb-Rh on silica: 100 psi hydrogen, S/C > 200, 0.1 molar in 2-propanol - water (1:1), room temperature, overnight; conditions for platinum oxide: 1 bar hydrogen, 5 mg catalyst per mmol substrate, 0.1 molar 2-propanol - water (1:1), room temperature, 30 mins; conditions for palladium on carbon (10%): 1 bar hydrogen, 5 mg catalyst per mmol substrate, 0.1 molar in 2-propanol - water (1:1), room temperature, 30 mins. [b] Determined by ¹H-NMR analysis after extraction of the crude reaction mixture with dichloromethane, drying (sodium sulfate) and evaporation. [c] Not detected by ¹H-NMR, GC or HPLC. [d] Reaction conditions: 100 psi hydrogen, 10 mg palladium on carbon (10%) per mmol substrate, room temperature, 1 hour. [e] Determined by HPLC analysis of the crude reaction mixture. [f] Reaction conditions: 1 bar hydrogen, 5 mg palladium on barium sulfate (5%) per mmol substrate, room temperature, 30 mins. [g] Detected by HPLC analysis of the crude reaction mixture. [h] Purchased from Fluka as a technical mixture of various amounts of monomers and oligomers. [i] Reaction conditions: 100 psi hydrogen, 10 mg palladium on carbon (10%) per mmol substrate, room temperature, 16 hours. [j] Reaction conditions: 100 psi hydrogen, S/C > 500, 60°C, 20 hours. [k] Reaction conditions: 100 psi hydrogen, S/C > 1000, 60°C, 24 hours. [l] Reaction conditions: 100 psi hydrogen, 10 mg platinum oxide per mmol substrate, room temperature, 16 hours.

CLAIMS

1. A supported catalyst comprising a cationic rhodium(I) complex of the formula

5



- wherein R¹ and R² are the same or different hydrocarbon groups of up to 30 C atoms, or
10 R¹ and R² are linked to form a ring, and a heterogeneous support medium that provides anionic binding sites.
2. A catalyst according to claim 1, wherein the support medium comprises a heteropolyacid anchoring agent.
3. A catalyst according to 2, wherein the heteropolyacid is of the Keggin type.
- 15 4. A catalyst according to claim 3, wherein the heteropolyacid is phosphotungstic acid, phosphomolybdic acid or silicotungstic acid.
5. A catalyst according to claim 4, wherein the heteropolyacid is phosphotungstic acid.
6. A catalyst according to any preceding claim, wherein the support medium
20 comprises an oxide selected from alumina, silica, titania, lanthana, zeolites and clays.
7. A catalyst according to claim 6, wherein the metal oxide is alumina.
8. A catalyst according to any preceding claim, wherein the support medium is a cation exchange resin containing sulphonic acid groups -SO₃⁻X⁺, wherein X⁺ is a proton or any other exchangeable cation.
- 25 9. A catalyst according to claim 8, wherein the cation exchange resin is a tetrafluoroethylene-perfluoro(vinyl ether sulfonate) copolymer.
10. A catalyst according to any preceding claim, wherein R¹ and R² are each an alkyl group.
11. A catalyst according to claim 10, wherein R¹ = R² = i-Pr.
- 30 12. Use of a catalyst according to any preceding claim, in a process of hydrogenating an aldehyde to produce the corresponding primary alcohol.

13. Use according to claim 12, wherein substrate conversion of at least 90% is effected, and wherein the aldehyde also contains at least one sulfide group that is retained in the product.
14. Use according to claim 12 or claim 13, wherein the process is carried out in a mixture of water and an alcohol.
5

INTERNATIONAL SEARCH REPORT

Internal Application No

PCT/GB 00/03851

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 B01J31/22 B01J31/28 C07C45/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 B01J C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BURK M J ET AL: "EFFICIENT RHODIUM-CATALYZED HYDROGENATION OF ALDEHYDES AND KETONES" 1994, TETRAHEDRON LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, VOL. 35, NR. 28, PAGE(S) 4963-4966 XP000465945 ISSN: 0040-4039 cited in the application the whole document ---	1-14
Y	WO 98 28074 A (SETON HALL UNIVERSITY) 2 July 1998 (1998-07-02) page 10, line 17 -page 11, line 3 page 14, line 20 -page 15, line 22 page 20, line 29 -page 21, line 30 ---	1-14
A	US 5 783 715 A (UGIN BENOIT) 21 July 1998 (1998-07-21) ----	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

7 December 2000

Date of mailing of the international search report

18/12/2000

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Schwaller, J-M

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal ref.	Application No
PCT/GB 00/03851	

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9828074	A 02-07-1998	AU 5710798 A		17-07-1998
		EP 0954375 A		10-11-1999
		US 6005148 A		21-12-1999
		US 6025295 A		15-02-2000
US 5783715	A 21-07-1998	AT 195525 T		15-09-2000
		CA 2170099 A		25-08-1996
		DE 59605736 D		21-09-2000
		EP 0729969 A		04-09-1996
		JP 8259584 A		08-10-1996
		US 5627293 A		06-05-1997

PCT

COPY REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired)(12 characters maximum)

REP06248WO

Box No. I TITLE OF INVENTION
SUPPORTED HOMOGENEOUS CATALYSTS FOR SELECTIVE HYDROGENATION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Chirotech Technology Limited
Cambridge Science Park
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CB4 0WG
United Kingdom

This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality: GB

State (that is, country) of residence: GB

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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1610 Nantucket Circle
Apartment 115
Santa Clara
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United States of America

This person is:

applicant only

applicant and inventor

inventor only *(if this check-box is marked, do not fill in below.)*

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: agent common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Gill Jennings & Every
Broadgate House
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United Kingdom

Telephone No.

+44 20 7377 1377

Facsimile No.

+44 20 7377 1310

Teleprinter No.

(051) 22765 GILPAT G

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III. FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

*If none of the following sub-boxes is used, this sheet is not to be included in the request.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GERLACH, Arne
 Chirotech Technology Limited
 Cambridge Science Park
 Milton Road
 Cambridge
 CB4 0WG
 United Kingdom

This person is:

- applicant only
 applicant and inventor
 inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*

DE

State *(that is, country) of residence:*

GB

This person is applicant
for the purposes of:

- all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address:

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

This person is:

- applicant only
 applicant and inventor
 inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*State *(that is, country) of residence:*This person is applicant
for the purposes of:

- all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address:

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

This person is:

- applicant only
 applicant and inventor
 inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*State *(that is, country) of residence:*This person is applicant
for the purposes of:

- all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

Name and address:

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

This person is:

- applicant only
 applicant and inventor
 inventor only *(if this check-box is marked, do not fill in below.)*

State *(that is, country) of nationality:*State *(that is, country) of residence:*This person is applicant
for the purposes of:

- all designated States all designated States except the United States of America the United States of America only the States indicated in the Supplemental Box

 Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LC Saint Lucia |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda | <input checked="" type="checkbox"/> LK Sri Lanka |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> BA Bosnia & Herzegovina | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BZ Belize | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MZ Mozambique |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DZ Algeria | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
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| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
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| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
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| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input type="checkbox"/> KZ Kazakhstan | |

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

-
-

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 08.10.1999 8 October 1999	9923952.7	GB		
item (2)				
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the Receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which the earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority).

Date (day/month/year) Number Country (or regional Office)

ISA/

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request	:	4
description (excluding sequence listing part)	:	10
claims	:	2
abstract	:	1
drawings	:	0
sequence listing part of description	:	0
Total number of sheets	:	17

This international application is accompanied by the item(s) marked below:

1. fee calculation sheet
2. separate signed power of attorney
3. copy of general power of attorney; reference number, if any:
4. statement explaining lack of signature
5. priority document(s) identified in Box No. VI as item(s):
6. translation of international application into (language):
7. separate indications concerning deposited microorganism or other biological material
8. nucleotide and/or amino acid sequence listing in computer readable form
9. other (specify): Patents Form 23/77

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

For the Applicant
Gill Jennings & Every

PERRY, Robert Edward

Date: 6 October 2000

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/		
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid		

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COPY
PATENT COOPERATION TREATY
PCT

NOTICE OF CONFIRMATION OF PRECAUTIONARY DESIGNATIONS
(to be filed with the receiving Office)
(PCT Rules 4.9(c) and 15.5)

Applicant's or agent's file reference REP06248WO	International filing date (day/month/year) 6 October 2000 (06.10.00)
International application No. PCT/GB00/03851	(Earliest) Priority date (day/month/year) 8 October 1999 (08.10.99)
Applicant Chirotech Technology Limited	

1. The applicant hereby confirms the following designations made under Rule 4.9(b):

Name of State (specify if a regional patent and/or another kind of protection or treatment is/are desired)

US

Name of Applicant(s) for that State

BURK, Mark Joseph
GERLACH, Arne

2. Prescribed fees (Applicants from certain States are entitled to a reduction of 75% of the designation fee and the confirmation fee. Where the applicant is (or all applicants are) so entitled, the total to be entered in the TOTAL box is 25% of the sum of the amounts entered at D and C. See Notes to the Fee Calculation Sheet as annexed to the Request Form, PCT/RO/101, for details.)

1	x	£56	=	£56	[D]
Number of designations confirmed		Amount of designation fee		Total designation fee	

Confirmation fee (50% of the above total) = £28 [C]

Total fees payable (D + C) = £84
TOTAL

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Mode of payment (payment must accompany this notice):

- | | | |
|--|---|---|
| <input type="checkbox"/> authorization to charge deposit account (see below) | <input type="checkbox"/> bank draft | <input type="checkbox"/> coupons |
| <input checked="" type="checkbox"/> cheque | <input type="checkbox"/> cash | <input type="checkbox"/> other (specify): |
| <input type="checkbox"/> postal money order | <input type="checkbox"/> revenue stamps | |

3. Signature of applicant or agent

PERRY, Robert Edward

Deposit account authorization

The RO/ is hereby authorized to charge the total fees indicated above to my deposit account.

is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number

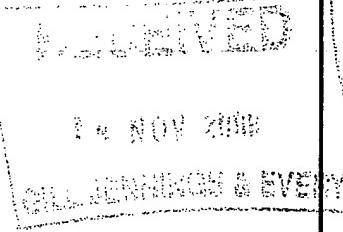
Date (day/month/year)

Signature

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To: Gill Jennings & Every Broadgate House 7 Eldon Street London EC2M 7LH	 2 NOV 2000
--	---

**NOTIFICATION REGARDING
CONFIRMATION OF
PRECAUTIONARY DESIGNATION**

(PCT Rules 4.9(c) and 15.5)

Date of mailing (day/month/year)	10/11/2000
-------------------------------------	------------

Applicant's or agent's file reference REP06248WO	IMPORTANT NOTIFICATION
International application No. PCT/GB00/03851	International filing date (day/month/year) 06/10/2000
Applicant Chirotech Technology-Limited et al	

1. Confirmation of precautionary designations made within 15 months from the priority date.

The applicant is notified that this receiving Office has received on: 2 November 2000
a notice of confirmation together with the payment of the prescribed fees for the designation of the following States:

- for an ARIPO patent (AP) (*specify "all States" or the two-letter country codes of the relevant States*) :
- all States for a Eurasian patent (EA)
- all States for a European patent (EP) (*specify "all States" or the two-letter country codes of the relevant States*) :
- all States for an OAPI patent (OA)
- for a national patent (*specify the States by indicating the two-letter country codes*) :
US

2. Incomplete or late notice of confirmation of precautionary designations.

The applicant is notified that this receiving Office has received on:
an attempted confirmation of precautionary designations. However, within 15 months from the priority date:

- no written notice of confirmation containing the indication of the designations to be confirmed was received
- no fees were paid
- the fees paid were insufficient to cover the designation and confirmation fees for the following designations:

Consequently, the designations concerned are, in accordance with Rule 4.9(b), regarded as withdrawn by the applicant.

3. No precautionary designation statement under rule 4.9(b) was made in the request.

Therefore the attempted confirmation of precautionary designations received on: 0 *bad date* 0
will not be taken into account and the designations concerned are not made.

4. Any overpayment (item 1) or any fees paid (item 2 or 3) will be refunded in due course.

5. The notice of confirmation together with a copy of this notification is being sent to the International Bureau.

Name and mailing address of the receiving Office The Patent Office Cardiff Road, Newport South Wales NP10 8QQ	Authorized officer Jenny Vaughan
Facsimile No.	Telephone No. 01633 814427

PATENT COOPERATION TREATY

General Authorisation

*I, GERLACH, Arne, of Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, United Kingdom

hereby appoint GILL JENNINGS & EVERY of Broadgate House, 7 Eldon Street, London EC2M 7LH, England (Telephone: +44 (0)20 7377 1377; Telex: 22765 GILPAT G; Fax: +44 (0)20 7377 1310) to act as agents on my behalf before the competent International Authorities in connection with any and all International applications filed by them with the British Patent Office as Receiving Office and to make or receive payments on my behalf.

Place: Cambridge, UK

Date: 30th October 2000

** 
Arne Gerlach

* When the Authorisation is given by a natural person, the family name should be indicated before the given name(s)

** When the Authorisation is given by a company, the name and status of the signatory should be typed under the signature

PATENT COOPERATION TREATY

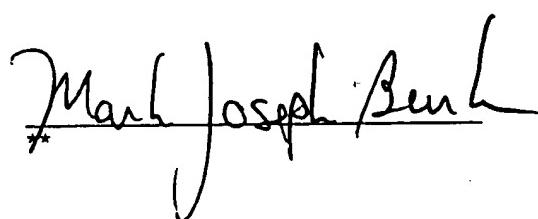
General Authorisation

I, BURK, Mark Joseph, of Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE, United Kingdom

hereby appoint GILL JENNINGS & EVERY of Broadgate House, 7 Eldon Street, London EC2M 7LH, England (Telephone: 0171-377-1377; Telex: 22765 GILPAT G; Fax: 0171-377-1310) as agents to act on my behalf before the competent International Authorities in connection with any and all international applications filed by them with the British Patent Office as Receiving Office and to make or receive payments on my behalf.

Place: Cambridge, England

Date: 30 March 1999



- * When the Authorisation is given by a natural person, the family name should be indicated before the given name(s)
- ** When the Authorisation is given by a company, the name and status of the signatory should be typed under the signature
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